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Treatment of Cancers

The present invention relates to the treatment of cancers.

BACKGROUND OF THE INVENTION

US Patent 5,089,273 relates to compounds identified as ecteinascidins. In particular, it relates to ecteinascidins 729, 743, 759A, 759B and 770. The compounds are disclosed to have antibacterial properties and some are also useful as antitumor agents.

SUMMARY OF INVENTION

We have now found that the potency of ecteinascidin 743 is enhanced by combination therapy with dexamethasone. The finding was not predictable.

According to the present invention, and based on this finding, we provide new ecteinascidin combinations for therapy of mammalian cancers, including:

combinations of ecteinascidins, notably ecteinascidin 743, with steroid analogues, in particular dexamethasone;

combinations of ecteinascidins, notably ecteinascidin 743, with anti-inflammatory drugs, in particular dexamethasone; and

combinations of ecteinascidins, notably ecteinascidin 743, with anti-emetic drugs, in particular dexamethasone.

Dexamethasone has many actions which include inducing the activity of certain metabolising enzymes of the liver. In particular, dexamethasone induces cytochrome P450 activity. Without being bound by theory, it is possible that metabolism of the ecteinascidin

743 by induced enzyme is giving rise to one or more metabolites which might be responsible for the enhanced effectiveness of the treatment with ecteinascidin 743.

Accordingly, we further provide:

combinations of ecteinascidins, notably ecteinascidin 743, with drugs inducing metabolic enzymes and in particular, cytochrome p450 enzymes;

Pharmaceutical formulations containing the combinations are also provided, as well methods of treatment using the combinations or using the compositions, as well as methods for preparing pharmaceutical compositions for use in the method of treatment. The drugs can be administered separately, sequentially or simultaneously.

PREFERRED EMBODIMENTS

The ecteinascidins as typified by ecteinascidin 743 have exceptional activity in the treatment of sarcomas, mesotheliomas, cartilage tumours and other cancers. Examples of human sarcomas to be treated include osteosarcomas and soft tissue sarcomas, leiomyosarcomas, fibrosarcomas and mesotheliomas.

Examples of pharmaceutical compositions of this invention include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compounds or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

Administration of the composition of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous administration. Intravenous delivery may be carried out over any suitable time period. We prefer that infusion times for the ecteinascidin of up to 24 hours are used, more preferably 2-12 hours, with 2-6 hours most preferred. Indeed, a typical time is about 3 hours. Short infusion times which allow treatment to be carried out without an overnight stay in hospital

are especially desirable. However, infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 2 to 4 weeks.

Pharmaceutical compositions containing ecteinascidins may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of the ecteinascidin will vary according to the particular formulation, the mode of application, and the particular *situs*, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The suitable amount of the other drug such as dexamethasone will also vary according to such principles. Illustratively a weight ratio of ecteinascidin:dexamethasone of from 2:1 to 5;1, such as 3.3:1 can be employed.

The combination compositions of this invention may be used with yet other drugs. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

a) drugs with antimitotic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);

b) antimetabolite drugs such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);

c) alkylating agents such as nitrogen mustards (such as cyclophosphamide or ifosphamide);

d) drugs which target DNA such as the antracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;

e) drugs which target topoisomerases such as etoposide;

f) hormones and hormone agonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuprorelin, goserelin, cyprotrone or octreotide;

g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;

h) alkylating drugs such as platinum drugs (cis-platin, carboplatin, oxaliplatin , paraplatin) or nitrosoureas;

i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;

j) gene therapy and antisense agents;

k) antibody therapeutics; and

l) other bioactive compounds of marine origin, notably the didemnins such as aplidine.

EXAMPLE

The sc B16 tumor model in male rats was used to compare dexamethasone pre-treated (3 mg/kg total dose; -15 min.), ET743 (90 μg/kg TD) animals to ET alone on a q2dx5, iv, schedule. Preliminary results on Day 14 show significant activity in the DEX-ET combination animals compared to ET alone. The following table gives the tumor volumes relative to controls and the BW indicating no significant toxicity with this combination.

Group	Dose	Schedule	Vol. (mm^3)	BW (grams)
Vehicle	-	q2dx5	18,862	216
DEX	0.60mg/kg	q2dx5	17,252	217
ET	0.018 mg/kg	q2dx5	15,243	198
DEX/ET	0.60 mg/kg (-24 hrs) DEX +0.018 mg/kg ET	q2dx5	6,653	170